# THE RETICULOENDOTHELIAL SYSTEM, CORTISONE, AND THYROID FUNCTION: THEIR RELATION TO NATIVE RESISTANCE TO INFECTION*

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While the ultimate nature of resistance to the chronic disease tuberculosis still remains elusive, there is little doubt that one of the most decisive factors in the progress of this disease is the fate of the bacilli within the mononuclear phagocytes, the reticuloendothelial cells. In the final analysis it is the response of these cells to the ingested microorganism, with or without the synergism of body fluids and the problematical humoral or cellular antibodies, that determines whether the result is an inapparent fleeting infection, or a fulminating and fatal tuberculosis, or a long-drawn-out, chronic disease with its alternating periods of remission and exacerbation. It is the purpose of this communication to integrate the host-parasite interactions of these cells and the spread of the bacilli from the portal of entry to the draining lymph nodes in untreated, highly inbred, natively resistant and susceptible rabbits, and the effects on these host-parasite relationships of cortisone and thyroidectomy, on the one hand, and hyperthyroidism, on the other, in inbred rabbits of uniform resistance.

## Materials and Methods

The model of quantitative airborne inhalation infection of human type tubercle bacilli H37Rv was used in rabbits of known different genetic resistance to tuberculosis.[1] The fate of the bacilli in the individual lesions in the lungs, in the draining lymph nodes, and in the spleen was studied, together with the correlated tissue responses at different intervals, from 1 day to 4 weeks after inhalation. In addition, in untreated, natively resistant and susceptible rabbits, these host-parasite relationships were investigated 2 months[2] and 1 year after infection.[3] It must be emphasized that, even in the most susceptible rabbits, the disease thus produced regressed and was not accompanied by systemic toxic manifestations. Similar procedures were used in the studies on the effects of cortisone administration[4,5] and alteration of thyroid function[6,7] on these host-parasite relationships. Needless to say, in each of these latter experiments the host-parasite relationships in untreated siblings of a given race and of a given genetic resistance were compared with those of cortisone-, triiodothyronine-, and thyroxine-treated, or thyroidectomized rabbits of the same race simultaneously exposed to the quantitative inhalation of the same aerosol of human tubercle bacilli.

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## Results

### *Host-Parasite Relationships in Untreated Natively Resistant and Susceptible Rabbits*

Figure 1 illustrates the fate of human-type tubercle bacilli in the lungs of the natively susceptible race C and of the natively resistant race III at different intervals after quantitative inhalation of human-type tubercle bacilli. On the ordinate are plotted logarithmically the ratio between the number of bacilli recovered from, and the number seeded in, the lungs at different intervals following infection. It is evident that, early in the course of the infection and

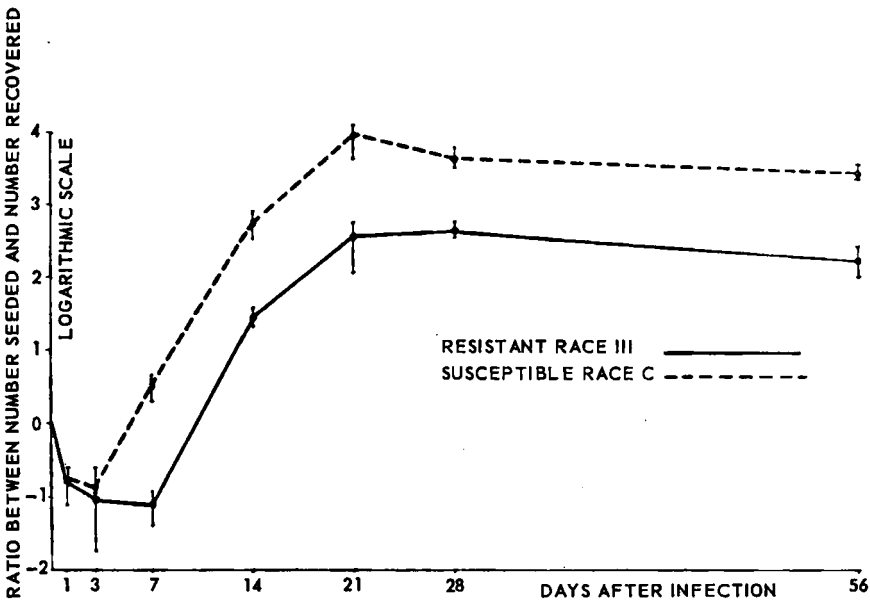


Figure 1. Population changes of human-type tubercle bacilli (H37Rv) in the lungs of natively resistant and susceptible rabbits at different intervals after quantitative airborne infection (treated culture).

long before specific acquired resistance becomes manifest, inbred, natively resistant rabbits inhibit the accumulation of inhaled human-type tubercle bacilli in the lungs 20 to 30 times more effectively than susceptible rabbits. Figure 2*a* and *b* demonstrate that, at the height of bacillary multiplication in the lungs of both races 2 weeks after infection, the reticuloendothelial cells (mononuclear phagocytes) of the resistant animals contain very many fewer organisms in their cytoplasm than these cells in the susceptible animals. Specific acquired immunity develops at the same time in both races, but its level is superimposed on, and quantitatively determined by, the initial native resistance. Thus even 1 year after infection, when the disease had regressed in both races, the residual viable bacilli are still twentyfold more numerous in the susceptible than in the resistant animal. The degree of healing in the

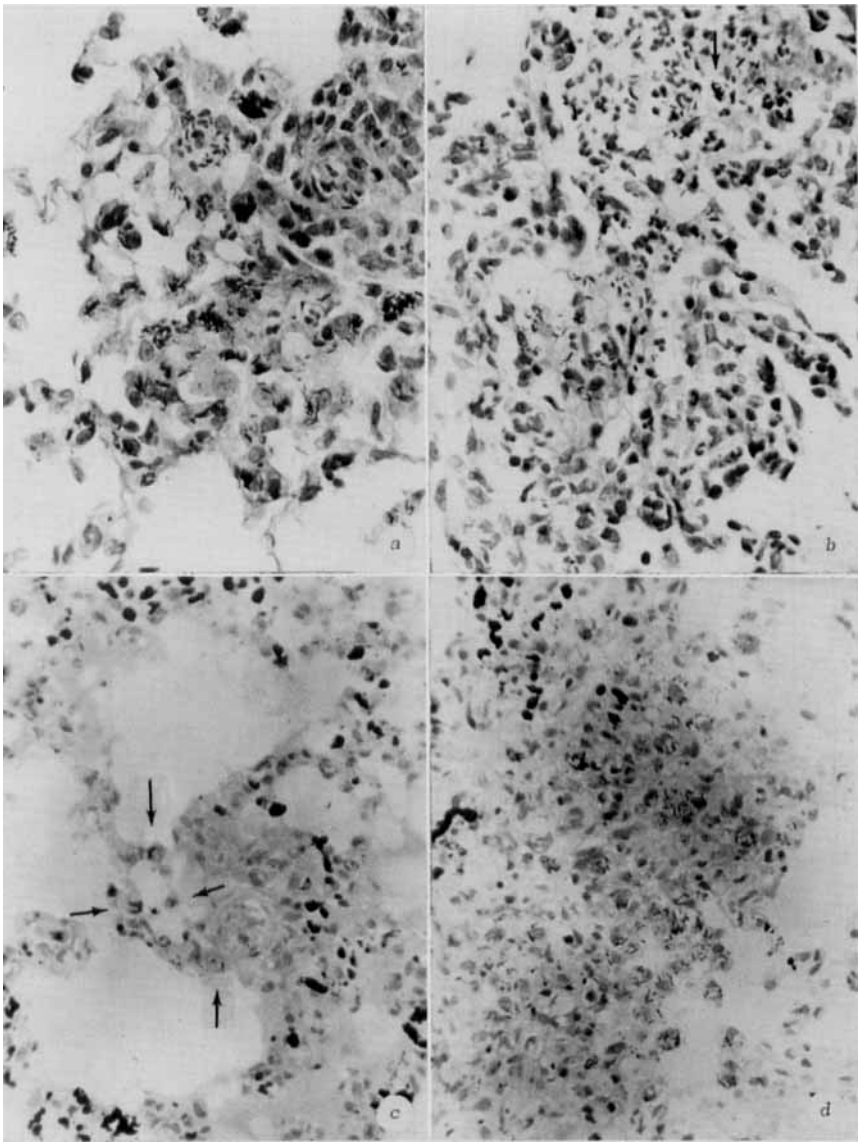

FIGURE 2. (*a*) A portion of an early tuberculous focus in the lung of susceptible rabbit Cl4-5 two weeks after the quantitative inhalation of an estimated 35,400 tubercle bacilli. Numerous tubercle bacilli, many of them in the form of very dense skeins, swarm in the intra-alveolar phagocytes. Perivascular accumulation of mononuclears, with some bacilli, is seen in the upper right corner. ×465. (*b*) An early tuberculous focus in the lung of resistant rabbit IIIR4-26 two weeks after the quantitative inhalation of 35,700 microorganisms. Moderate numbers of tubercle bacilli are seen in the intra-alveolar phagocytes. Only one small skein, indicated by the arrow, can be seen in the upper alveolar space, which is infiltrated by numerous polymorphonuclear leukocytes. ×465. (*c*) Primitive lesion in untreated rabbit Ca5-10 two weeks after quantitative inhalation of tubercle bacilli. The arrows indicate the meager numbers of microorganisms within the phagocytes. ×360. (*d*) Primitive lesion in the lung of Ca5-9, a cortisone-treated littermate of Ca5-10, shown in *c*, two weeks after inhalation. Numerous intracellular bacilli are found within the phagocytes. ×360.

2 races at this time is of a corresponding order.[3] It is noteworthy that the maturation of mononuclear phagocytes into epithelioid cells, a transformation that is uniformly associated with the diminution of the ingested bacilli, is much more rapid in the natively resistant rabbit,[2] indicating that the acquired immunity is conditioned by the native resistance and is more effective in genetically resistant animals.

Significantly, the spread of the bacilli from the portal of entry (the lung) to the draining lymph nodes is, contrary to expectation, enhanced in the resistant rabbit. FIGURE 3 illustrates this difference. Thus, while 20 per cent of the bacilli present in the lung were recovered from the lymph nodes of the resistant

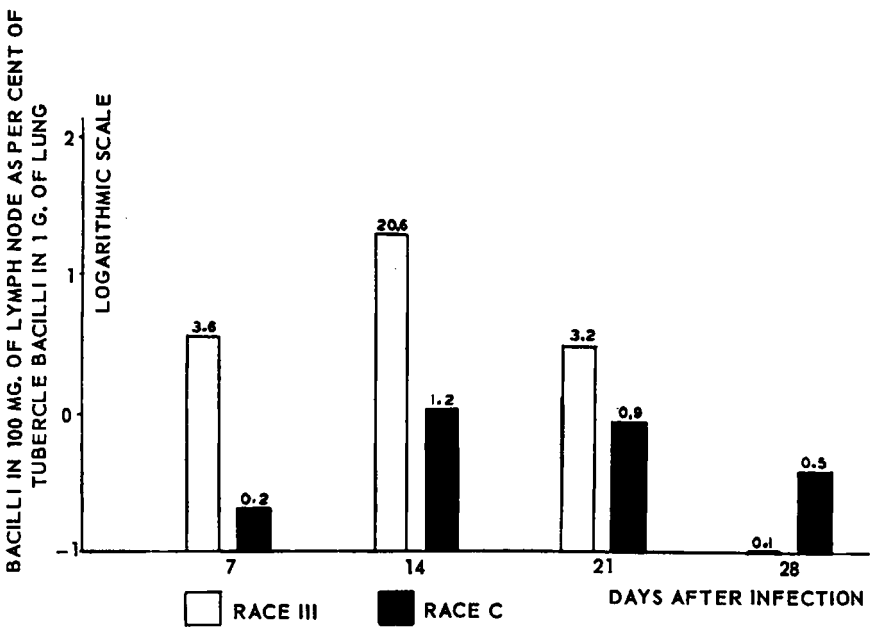


FIGURE 3. The percentage of human-type bacilli from the lungs that were recovered from the draining lymph nodes in resistant race III and susceptible race C rabbits.

animal 2 weeks after infection, only 1 per cent of the bacilli present in the lungs of the susceptible animal were recovered from its draining nodes. Four weeks after infection, however, the bacilli in the nodes of resistant rabbits had been reduced to one twenty-sixth of the number present in these nodes on the third week after infection, whereas the bacilli in these nodes in the susceptible animal were reduced by only one half in the same interval. It is evident that, while the bacilli in the resistant animal are disseminated from the portal of entry to a greater degree than in the susceptible, their growth is much more effectively inhibited in the metastatic foci of the former.

### *Host-Parasite Relationships in Cortisone-Treated Rabbits*

While it is generally accepted that the administration of certain amounts of cortisone and its variants markedly reduces the resistance of many species

to a variety of infections, there is no agreement on the mode of action of this hormone in this relation. The most widely held hypothesis claims that the anti-inflammatory effect of the steroid enhances the disease and its spread.[8] In the infection of rabbits by the quantitative inhalation of human-type bacilli, however, it was demonstrated that, far from enhancing the spread of the bacilli from the portal of entry to the draining lymph nodes, cortisone markedly retards their dissemination.[4] This is illustrated in FIGURE 4. The lowered

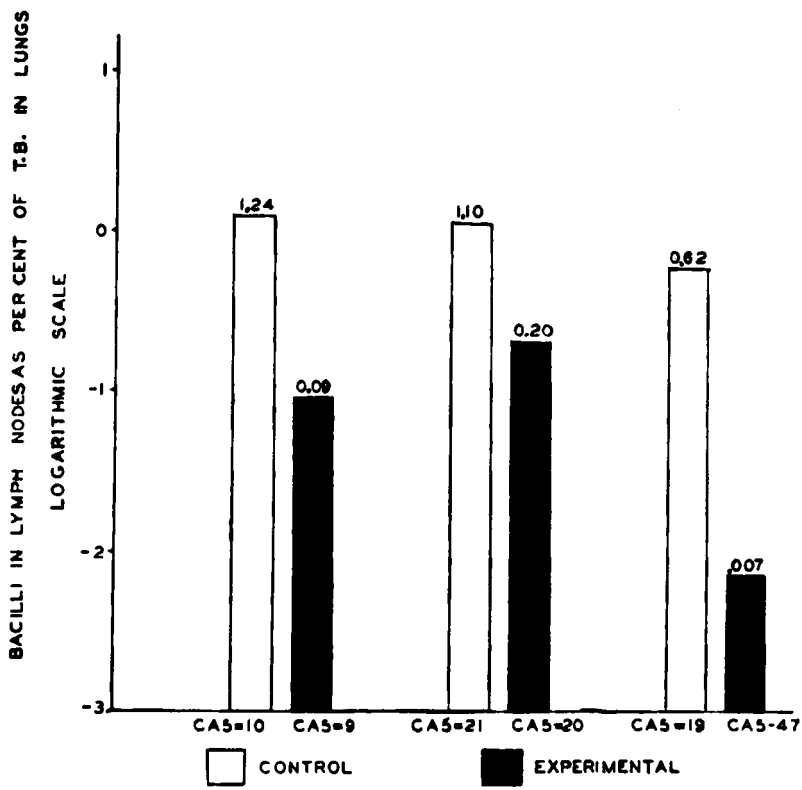


FIGURE 4. The percentage of human-type bacilli from the lungs that were recovered from the draining lymph nodes of cortisone-treated and control susceptible race CA rabbits 2 weeks after infection by inhalation.

resistance of the steroid-treated animals is apparently associated with a deprivation of the reticuloendothelial cells (mononuclear phagocytes) of much of their innate capacity to inhibit the growth of tubercle bacilli within their cytoplasm. This is illustrated in FIGURE 2*c* and *d*. Furthermore, cortisone retards the maturation of tubercle bacilli-infested mononuclears into epithelioid cells,[5] which again testifies to the reduced capacity of these reticuloendothelial cells to inhibit the growth of the bacilli in their cytoplasm. Similar observations by Thomas,[9] Kass *et al.*,[10] and Cremer and Watson[11] suggest that steroids impair the function of the reticuloendothelial system (RES) in eliminating or detoxifying bacteria, certain of their products, and other phagocytized material. That

a correspondence exists between the direct action of adrenocortical hormones on cultured cells and their action in the organism has been demonstrated by Grossfeld.[12]

The difference in host-parasite relationships between a cortisone-treated rabbit and an untreated sibling of the same genetic resistance is of a similar general nature as that between an untreated natively susceptible and untreated natively resistant animal. In both instances reduced resistance is associated with a reduced ability of RES to inhibit the intracellular growth of the bacilli,

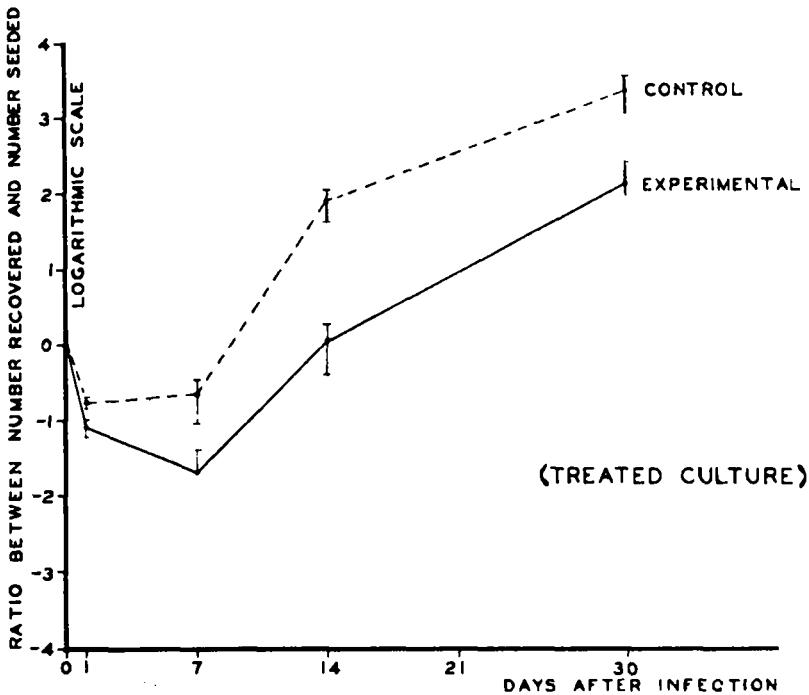


FIGURE 5. The effect of TIT on population changes of human-type bacilli (H37Rv) in the lungs of AD rabbits at different intervals after quantitative airborne infection.

a retardation in the maturation of epithelioid cells, and a diminution in the spread of the bacilli from the site of invasion.

### *Host-Parasite Relationships in Triiodothyronine- and Thyroxine-Treated and in Thyroidectomized Rabbits*

Since hyperthyroidism increases the metabolic cellular activity, an investigation into the effect of thyroid function on native resistance was undertaken. It was found that hyperthyroidism induced by L-triiodothyronine (TIT) or L-thyroxine markedly increased the native resistance to the inception and progress of the disease in 4 different inbred races of rabbits, chiefly of intermediate genetic resistance to the disease.[6] The increment in resistance afforded by TIT to the most susceptible race in our colony (C) was discernible, although

slight. FIGURE 5 demonstrates that the increased resistance afforded by triiodothyronine is due to the marked suppression of the accumulation of tubercle bacilli in the lungs of the hormone-treated animals. FIGURE 6 shows that the transport of bacilli from the portal of entry to the draining lymph nodes is enhanced in the hyperthyroid rabbits.

Similar observations were made on some of these races treated with L-thyroxine. The reduction of bacillary accumulation in the lungs produced by

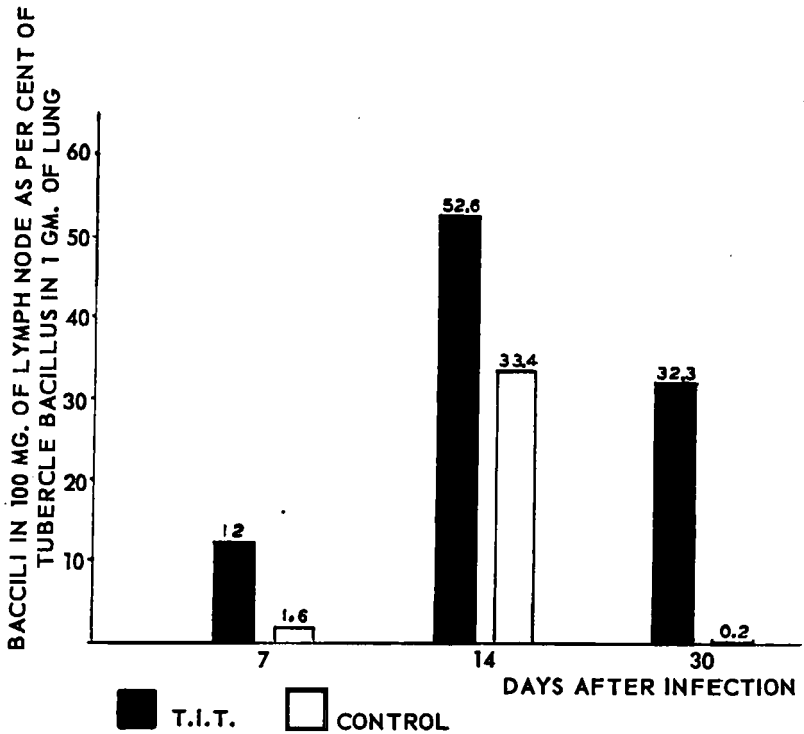


FIGURE 6. The percentage of human-type tubercle bacilli from the lungs that were recovered from the draining lymph nodes of TIT-treated and control race AD rabbits of intermediate resistance.

thyroxine is illustrated in FIGURE 7, and the inhibition of bacillary growth within the reticuloendothelial cells of the lung is depicted in FIGURE 8*a* and *b*.

Thus, hyperthyroidism increases the resistance of a given race in the same manner as natively resistant animals restrict the disease more than the natively susceptible animals. In both instances the increased resistance is brought about by an augmentation of the inhibitory capacity of reticuloendothelial cells against the accumulation of the bacilli within their cytoplasm and, consequently, a more rapid maturation of epithelioid cells. Associated with this increment in resistance in the hyperthyroid rabbit is an enhancement of the spread of the bacilli from the site of invasion, a relationship similar to that in natively resistant rabbits.

The converse of the above is produced by suppressing thyroid function with propylthiouracil or thyroidectomy.[7] FIGURE 9 shows that the accumulation of tubercle bacilli in the lungs of the thyroidectomized IIIA rabbits is 10 times greater than in their intact siblings exposed simultaneously to the quantitative inhalation of the same aerosol of human bacilli. FIGURE 8*c* and *d* shows that thyroidectomy deprives the reticuloendothelial cells of much of their innate capacity to inhibit the growth of the bacilli within their cytoplasm. Associated with this reduction of inhibition of intracellular multiplication is a retardation

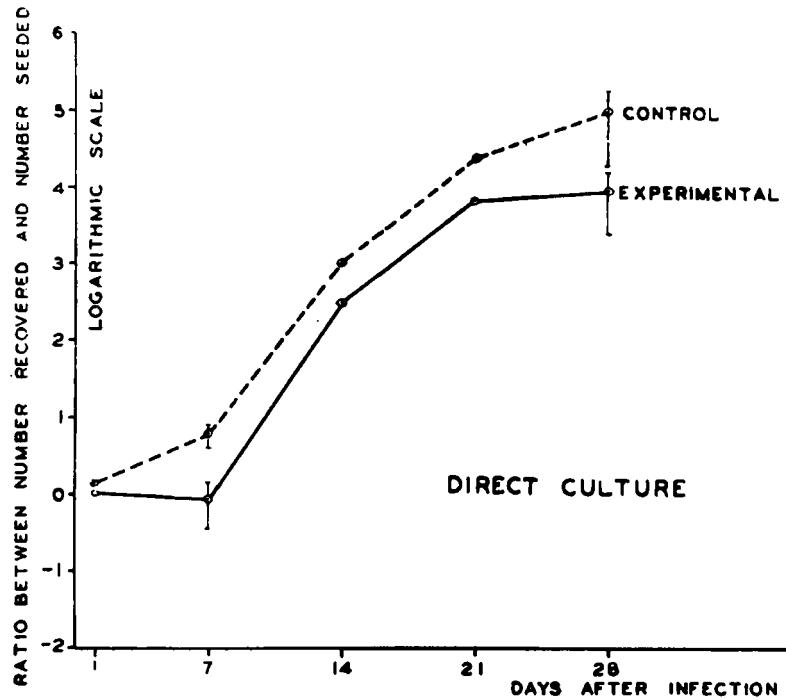


FIGURE 7. The effect of L-thyroxine on population changes of human-type bacilli (H37Rv) in the lungs of III IIIC rabbits at different intervals after quantitative airborne infection.

in the maturation of epithelioid cells and a marked diminution of the transport of the bacilli from the portal of entry to the draining lymph nodes as contrasted with their behavior in intact siblings of the same genetic resistance, as illustrated in FIGURE 10.

Thus, thyroidectomy induces host-parasite relationships similar to those obtaining in untreated natively susceptible rabbits and in cortisone-treated animals. In all these instances lowered resistance is associated with a reduced capacity of the reticuloendothelial cells to suppress the growth of the bacilli in their cytoplasm, a slower maturation of epithelioid cells, and a retardation in the spread of the bacilli from the portal of entry.

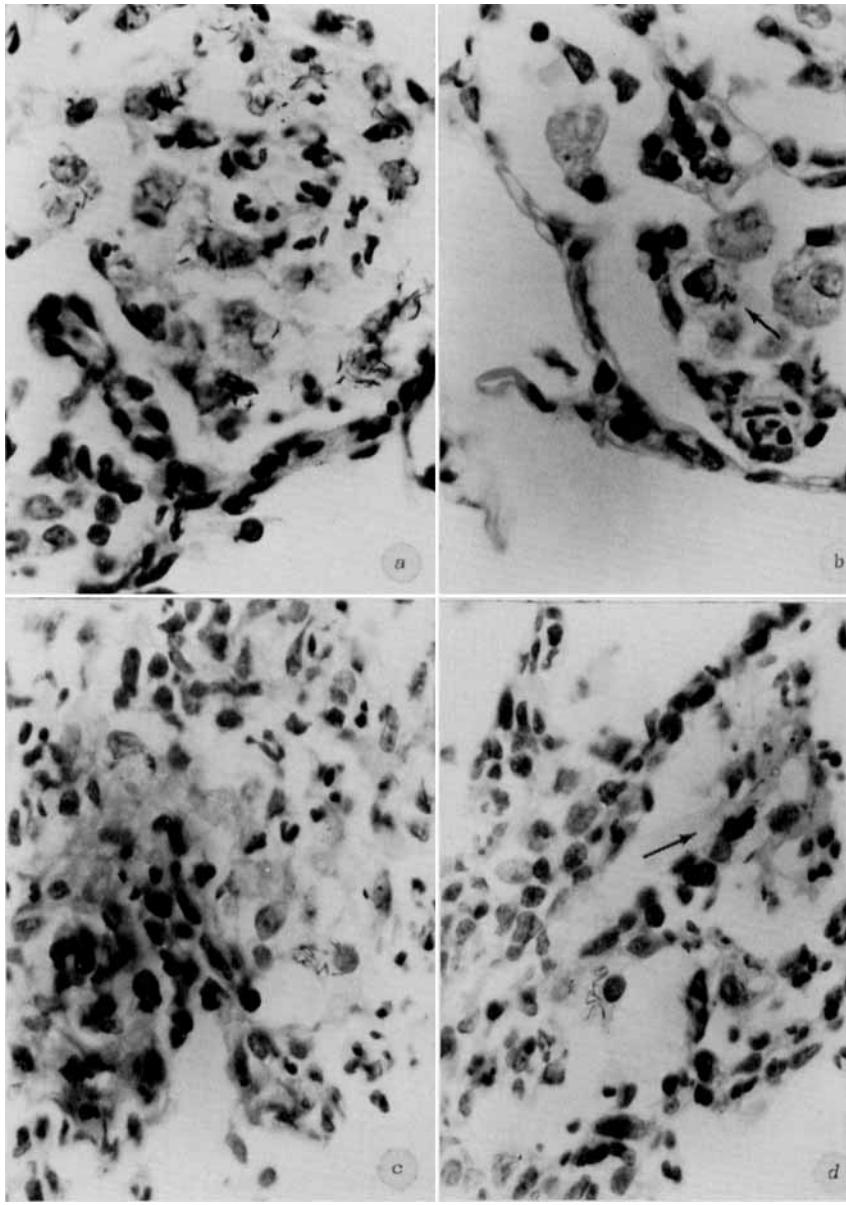

FIGURE 8. (*a*) Primitive tuberculous focus in control rabbit III IIIC4-11, two weeks after the inhalation of 9,000 bacilli. Note the numerous tubercle bacilli within alveolar phagocytes and the single skein of microorganisms near the lower edge of the alveolar space. The bacilli in this lung had multiplied two thousandfold over those seeded. ×747. (*b*) Primitive tuberculous focus in the thyroxine-treated rabbit III IIIC4-10, a sibling of III IIIC4-11, shown in *a*, 2 weeks after the inhalation of 18,000 bacilli. A rare bacillus within an alveolar phagocyte is indicated by the arrow. The bacilli in this lung had multiplied 61 times over those seeded. ×747. (*c*) Primitive tuberculous focus in the lung of intact rabbit IIIA5=4, two weeks after inhalation of 8,800 bacilli. An occasional alveolar phagocyte contains some bacilli. The bacilli in this lung had multiplied ninety-sixfold over the number seeded. There is extensive interstitial mononuclear infiltration to the left of the alveolar space. ×747. (*d*) Primitive tuberculous focus in the lung of thyroidectomized rabbit IIIA5=3, a sibling of IIIA5-4 shown in *c*, two weeks after the inhalation of 7,900 bacilli. There are numerous bacilli within the alveolar phagocytes. A very dense skein of tubercle bacilli within one such phagocyte is indicated by the arrow. The bacilli in this lung had multiplied five hundred and sixty-eightfold over the number seeded. There is very slight thickening of the septum surrounding this alveolar space. ×747.

*Phagocytic Activity and Antibody Production of Reticuloendothelial Cells in Rabbits of Different Degrees of Native Resistance, in Cortisone-Treated, and in Hyperthyroid and Hypothyroid Rabbits*

Contrary to expectation, natively highly resistant race III rabbits cleared their blood stream of colloidal carbon much more slowly than did susceptible rabbits of the C or FC strains. This clearance was measured by the method of Benacerraf[13] with uniform carbon particles kindly furnished us by J. H. Heller of the New England Institute for Medical Research, Ridgefield, Conn., and B. Benacerraf, of New York University, New York, N. Y., and adminis-

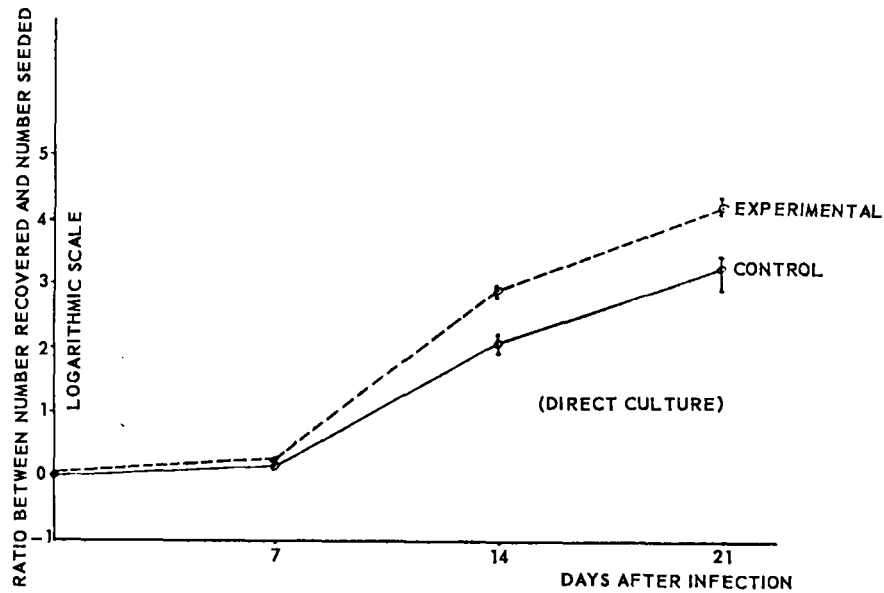


FIGURE 9. The effect of thyroidectomy on population changes of human-type bacilli (H37Rv) in the lungs of race IIIA rabbits at different intervals after quantitative airborne infection.

tered intravenously in doses of 5 mg./100 gm. body weight. Cortisone uniformly retarded the blood clearance, while hyperthyroidism induced by TIT and hypothyroidism induced by thyroidectomy appeared to have no effect. Thus there was no constant relationship between the phagocytic avidity of the RES for these particles and the fate of tubercle bacilli ingested by reticuloendothelial cells.

However, there seems to be a fairly constant correlation between resistance to infection and the capacity to form antibodies. Hyperthyroidism induced by TIT tends to increase antibody formation, as indicated by the amount of antibody nitrogen formed early after primary or secondary immunization with bovine serum albumin. On the other hand, thyroidectomy definitely and significantly retarded and depressed antibody formation to this antigen. It is well known that cortisone suppresses antibody production by the RES.

While there is no strict parallel between the degree of native resistance and the capacity for antibody formation, there is a tendency in this direction. Thus the very susceptible race FC rabbit produces very low antibody titers as compared with the more resistant races AD or III.[7] Thus the increased inhibition of bacillary accumulation within the reticuloendothelial cells is

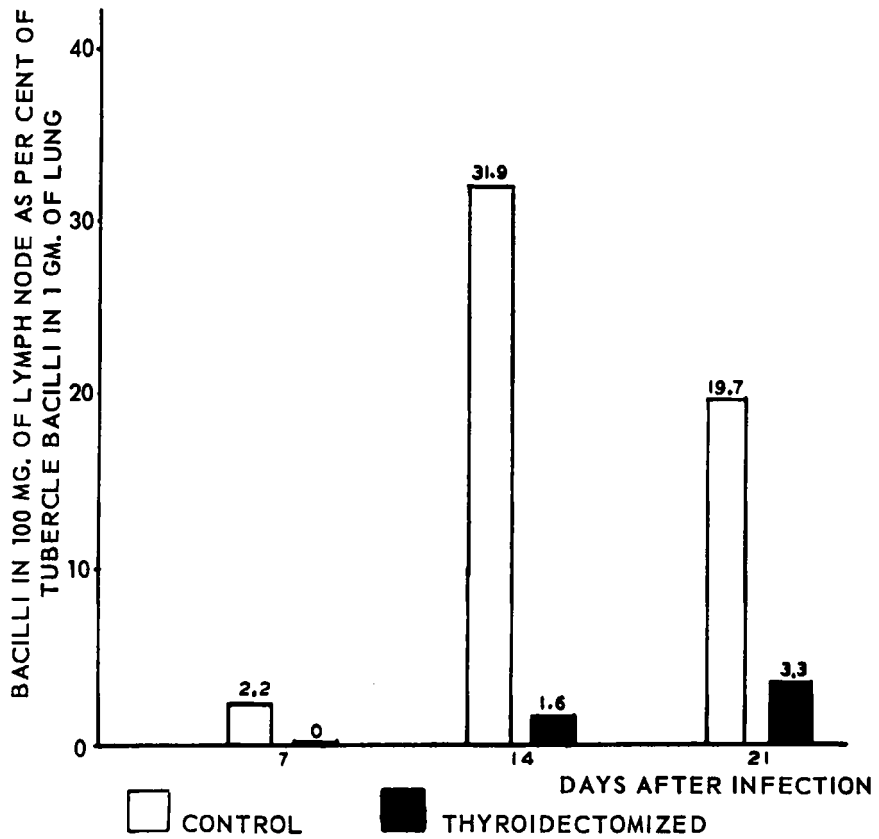


FIGURE 10. The percentage of human-type bacilli from the lungs that were recovered from the draining lymph nodes of thyroidectomized and control race IIIA rabbits of intermediate resistance.

generally associated with an increased capacity for antibody formation against antigens in general. If antibody formation is considered a function of reticuloendothelial cells, then these data would lend additional support to the concept that increased resistance, whether afforded by the native constitution or induced by hyperthyroidism, is an expression of the increased activity of these cells and, conversely, reduced resistance, whether determined by genetic factors or following the administration of cortisone or the induction of hypothyroidism, is a consequence of the reduced reticuloendothelial cell activity.

## Discussion

It seems clear from the foregoing that there are certain host-parasite relationships that characterize resistance and certain others that characterize susceptibility. Increased resistance, whether due to constitutional factors or to added thyroid treatment, is associated with an enhanced capacity of the reticuloendothelial cells to inhibit the multiplication of the bacilli in their cytoplasm *in vivo*, a more rapid maturation of reticuloendothelial cells into epithelioid cells, a generally increased capacity for antibody formation, and a greater dissemination of the bacilli from the portal of entry in the lung to the draining lymph nodes. On the other hand, susceptibility, whether due to inherent genetic factors or induced by thyroidectomy or the administration of cortisone, is associated with a reduced capacity of the reticuloendothelial cells to inhibit the growth of the bacilli in their cytoplasm, a retardation in the maturation of epithelioid cells, a reduced capacity for antibody formation, and a diminished spread of the bacilli from the site of invasion to the draining nodes.

Most of the differences in the host-parasite relationships between resistant and susceptible states appear to stem from differences in the degree of activity of the reticuloendothelial cells; the greater the resistance, the greater the physiological activity. It is noteworthy, therefore, that the increased resistance to reinfection was associated, as early as 1939,[14] with a nonspecific increment of the physiological activity of the reticuloendothelial cells, as evidenced by their increased *in vitro* phagocytic activity for nonspecific particles and their increased propensity for division in response to stimuli applied *in vivo*. That phagocytes derived from immunized animals, without the aid of humoral antibodies, have a greater capacity to inhibit intracellular growth of tubercle bacilli than those derived from normal rabbits has been demonstrated by us with the *in vivo* eye chamber technique and confirmed in tissue culture studies with isolated cells by a number of observers for tubercle bacilli and *Brucella* infection,[15-18] although not by all. No studies have yet been reported on whether reticuloendothelial cells derived from natively resistant animals inhibit the growth of tubercle bacilli *in vitro* to a greater degree than such cells derived from susceptible animals, nor is there authentic evidence that macrophages derived from cortisone-treated animals suffer from a reduced capacity to inhibit the growth of bacteria in their cytoplasm *in vitro*. However, Hsu and Kapral[19] seem to have found that mononuclear phagocytes derived from guinea pigs treated with TIT suppress the growth of virulent human-type tubercle bacilli *in vitro* to a much greater degree than those derived from untreated animals.

That the maturation of mononuclear phagocytes into epithelioid cells is associated with the diminution of the ingested bacteria has been long established by us, and no evidence against this view has been presented.

That genetic resistance is associated with an increased capacity for antibody formation has been reported by numerous investigators as well as by ourselves.[20-22] Long and Shewell[23] have reported that thyroxine markedly increased the production of diphtheria antitoxin in guinea pigs. Hyperthyroidism induced by TIT increases antibody formation against bovine serum albumin.[7] This observation has been confirmed by Trapani *et al.*[24] Dixon

*et al.*[25] first observed that thyroxine reduces the half life of $\gamma$ globulin in rabbits from 4.6 to 3.2 days. It is understandable, therefore, that the rate of decline of antibody nitrogen in the serum after it reaches its peak is more rapid in the hyperthyroid than in the euthyroid animal. Conversely, our observations on the reduction in antibody formation by thyroidectomy have also been confirmed by Trapani and his co-workers, who also found that the half life of passively administered antibody is twice as long in thyroidectomized as in euthyroid rabbits.[24] Correspondingly, the decay of antibody in the serum after reaching its height is slower in the thyroidectomized than in the intact rabbit.[7] That cortisone diminishes antibody formation is generally accepted. It is thus seen that there is a close correlation between resistance and the antibody-forming capacity of reticuloendothelial cells.

Contrary to expectation, the spread of the bacilli from the pulmonary portal of entry to the draining nodes is greater in the natively resistant than in the natively susceptible rabbit. Correspondingly, the spread of the bacilli from the site of invasion to these nodes is enhanced by hyperthyroidism and reduced by cortisone treatment or thyroidectomy. These observations are in line with the concept of Miles and Miles[26] that one mechanism by which resistance is increased is the diminution of the local effects of noxious agents by dispersing them among humoral or cellular protective entities beyond the site of entry. I pointed out many years ago[27] that the allergic inflammation in immunized rabbits accelerates the spread of the bacilli from the site of reinfection.

Obviously, the spread of bacilli from the portal of entry to the draining lymph nodes, whether free or within phagocytes, is controlled by the lymph flow, which in turn is influenced by the degree of inflammation. The more intense the nonnecrotizing inflammation, the greater the lymph flow and, consequently, the greater the bacillary transport. While there is some relation between the nonspecific inflammatory irritability and resistance, it is not constant. Thus cortisone and thyroidectomy both reduce inflammation. The inflammatory response to turpentine is greater in the resistant rabbit race III than in the susceptible race C. However, no evidence is at hand to indicate that the inflammatory irritability in hyperthyroid rabbits is greater than in euthyroid animals, but the spread of the bacilli from the portal of entry to the draining nodes is greater in the former. It is postulated that the increased inhibition of bacillary accumulation within the reticuloendothelial cells characteristic of increased resistance may be associated with the release of inflammatory irritants, possibly derived from the surface of the bacteria,[28] which increase lymph flow and thus enhance the dissemination of the infectious agent and its "dilution" in the sense of Miles and Miles.[26]

At first glance, the increased resistance afforded rabbits quantitatively infected by inhalation of human tubercle bacilli appears to be at variance with a number of observations on hyperthyroid mice, in which the mortality from a variety of acute infections, including tuberculosis, was increased by TIT or thyroxine.[29-31] However, as pointed out by Smith and Dubos,[32] this increased mortality was not due to an enhancement of bacterial proliferation, but rather to a possible increased susceptibility of the hyperthyroid mice to toxins and other bacterial products. In fact, it has since been demonstrated by Melby

and Spink[33] and Bradley and Spink[34] that hyperthyroidism enhances the lethal action of endotoxins in mice; hence the greater mortality of hyperthyroid mice from acute infection. The model infection under scrutiny in the present study does not involve the death of the animal but the intimate host-parasite relations of the individual lesions that tend to regress and are not associated with lethal toxic phenomena.

Of great interest in this relation are the observations of Halpern and his coworkers[35] on mice, Suter's studies in guinea pigs[36] and, particularly, those of Howard *et al.* in mice.[37] All of these investigators have shown that in animals vaccinated with BCG or treated with zymosan[38] the lethal toxicity of endotoxin is increased one hundredfold. At the same time, however, there is evidence of activation of the RES, not only from the standpoint of its capacity to clear the circulation of carbon particles but, even more significantly, from the standpoint of its affording increased resistance against the multiplication of bacteria within its reticuloendothelial cells. Thus a parallel is established between hyperthyroidism and BCG vaccination; both increase the lethal effects of endotoxins, yet both increase the bacteriostatic activity of the RES cells. On the other hand, cortisone, which suppresses the bacteriostatic effects of the reticuloendothelial cells, can protect mice from the lethal effects of endotoxin.[39-41] It is well known that hyperthyroidism potentiates the physiological effects of epinephrine.[42] It is also generally held that the lethal effects of endotoxin are partly due to its profound effects on the vascular system, presumably by changing the reaction of smooth muscle to epinephrine and norepinephrine.[43] Whether the action of these or other vasoactive drugs can explain how BCG vaccination or the induction of granuloma by zymosan increases toxicity to endotoxin or, conversely, why cortisone is protective against endotoxin, and how the function of the RES mediates these effects, are problems that remain to be determined.

## Summary

Early in the course of infection, and long before specific acquired resistance develops, inbred natively resistant rabbits inhibit the accumulation of inhaled human-type tubercle bacilli within the pulmonary reticuloendothelial cells (mononuclear phagocytes) 20 to 30 times more effectively than susceptible animals. Significantly, the spread of the bacilli from this portal of entry to the draining lymph nodes is enhanced, contrary to expectation, in the resistant rabbit. Cortisone deprives these phagocytes of much of their innate capacity to inhibit the multiplication of the bacilli in their cytoplasm, and thus markedly lowers resistance. Cortisone treatment also is associated with a retardation in the transport of the bacilli from the site of invasion. These host-parasite relationships are characteristic of untreated susceptible rabbits. Hyperthyroidism induced by thyroxine or TIT markedly suppresses the accumulation of the bacilli within the alveolar phagocytes, increases resistance, and enhances the lymphatic spread of the bacilli, as in untreated natively resistant rabbits. Thyroidectomy, like cortisone, enhances the accumulation of the bacilli within the mononuclear phagocytes, lowers resistance, and retards the dissemination of bacilli from the portal of entry. Increased resistance, whether native or induced by hyperthyroidism, is associated with a rapid maturation into epithe-

lioid cells of mononuclear phagocytes that had ingested tubercle bacilli. Reduced resistance, whether native or induced by cortisone or thyroidectomy, is associated with a retardation in the maturation of mononuclear phagocytes into epithelioid cells. Antibody production tends to be increased in natively resistant as compared with natively susceptible animals. Hyperthyroidism has a similar effect, while cortisone and thyroidectomy definitely retard and depress antibody formation.

In contrast to similar experiments done in several other laboratories, the infection used in these studies in the rabbit leads to regressive lesions without generalized lethal toxic phenomena. Under these conditions hyperthyroidism increases resistance. The reduction in survival of hyperthyroid mice with acute infections is discussed and is interpreted as the expression of the increased lethal effects of endotoxins in this state.

It is concluded that resistance to tuberculosis is to a great extent a function of the physiological activity of the reticuloendothelial cells, that the degrees of native resistance are determined by the level of activity of these cells, that hyperthyroidism increases resistance by increasing the activity of these cells, and that thyroidectomy or the administration of cortisone lowers resistance by depressing the function of these cells.

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